CERTIFICATE OF MAILING Via facsimile 703-308-4556			
I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.			
Typed or Printed Name	Donna Macedo		
Signature	D. Macedo	**Date**	12/10/02

DECLARATION UNDER 37 C.F.R. § 1.132 Address to: Assistant Commissioner for Patents Washington, D.C. 20231	Attorney Docket Confirmation No.	CALD-006 4890
	First Named Inventor	Galer et al.
	Application Number	09/775,592
	Filing Date	January 5, 2001
	Group Art Unit	1614
	Examiner Name	Cook, R.
	Title	*Methods for Treating Indomethacin Responsive Headaches*

Sir:

I, Lawrence C. Newman, M.D., am a co-inventor of the above referenced application. Enclosed is a copy of my Curriculum Vitae which demonstrates that I am qualified to speak on the level of one of skill in the art.

I hereby declare the following:

Prior to my work in this area as embodied in the present application and claims, it was my expectation, which is the same as with what those of skill in the art would expect, that a topical formulation of indomethacin would not be able to supply **therapeutically effective levels of indomethacin** to be able to successfully treat indomethacin-responsive headaches. As such, prior to my work in this area, the methods of treating indomethacin-responsive headaches involved only oral and rectal administration of indomethacin, because it was believed that only oral and rectal formulations (not topical formulations) could supply sufficient levels of indomethacin to treat indomethacin-responsive headaches. Thus at that time, there was an extremely low expectation of success that a topical formulation of indomethacin could supply a

therapeutically effective amount of indomethacin to successfully treat indomethacin-responsive headaches.

The present application and claims are based on our discovery of the unexpected result that a topical formulation of indomethacin provides a therapeutically effective method of treating indomethacin-responsive headaches.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code; and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 12/9/02

Signature: _____
Lawrence C. Newman, M.D.

Encl.

* C.V. of Lawrence C. Newman, M.D.

F:/Document/Cald/006/Declaration of Newman

CURRICULUM VITAE

LAWRENCE C. NEWMAN, M.D.
ST. LUKE'S-ROOSEVELT HOSPITAL CENTER
AND
BETH ISRAEL MEDICAL CENTER
1000 TENTH AVENUE
NEW YORK, NEW YORK 10019
(212) 523-5869
Fax: (212) 523-5902

DATE OF BIRTH:

January 10, 1958

EDUCATION:

1979	Clark University, Worcester, Massachusetts	B.A.
1983	Universidad Autonoma de Guadalajara, Guadalajara, Jalisco, Mexico	M.D.

POST-GRADUATE EDUCATION:

1984-1985	Fifth Pathway, Elmhurst Hospital Center, Elmhurst, New York
1985-1986	Resident, Department of Internal Medicine, Elmhurst Hospital Center Elmhurst, New York
1986-1989	Resident and Chief Resident, Neurology, Albert Einstein College of Medicine Bronx, New York
1989-1990	Headache Fellow, Headache Unit, Montefiore Medical Center, Bronx, New York

PROFESSIONAL EMPLOYMENT

1988-1996	Staff Neurologist and Research Associate, Headache Unit
1989-1991	Assistant Attending Physician, Montefiore Medical Center, Bronx, New York
1989-1991	Assistant Attending Physician, Bronx Municipal Hospital Center, Bronx, New York
1989-1992	Assistant Attending Physician, Hospital of the Albert Einstein College of Medicine, Bronx, New York
1989-1992	Instructor of Neurology, Albert Einstein College of Medicine, Bronx, New York York
1989-1992	Neurology Consultant, Teaching Nursing Home Study, Albert Einstein College of Medicine, Bronx, New York

PROFESSIONAL EMPLOYMENT (continued):

1990-1992	Deputy Director, Neurology, Montefiore Medical Center, Bronx, New York
1990-1996	Co-Director, Montefiore Manhattan Headache Unit, New York, New York
1991-1999	Assistant Professor of Neurology, Albert Einstein College of Medicine, Bronx, New York
1999-	Associate Clinical Professor of Neurology, Albert Einstein College of Medicine, Bronx, New York
1991-	Attending physician, Neurology, Montefiore Medical Center, Bronx, New York
1996-1996	Co-Director, Montefiore Headache Unit, Bronx, New York
1996-1998	Director, Montefiore Manhattan Headache Unit, New York, New York
1996-1997	Director, Montefiore Headache Unit, Bronx, New York
1996-	Faculty member, Women's Health Tract, Albert Einstein College of Medicine
1998-	Director, The Headache Institute at St. Luke's-Roosevelt Hospital and Beth Israel Medical Centers, New York, New York
1998-	Attending physician, Department of Neurology, St. Luke's-Roosevelt Hospital Center, New York, New York
1998-	Attending physician, Department of Neurology, Beth Israel Medical Center, New York, New York
1998-	Attending physician, Department of Pain Medicine and Palliative Care, Beth Israel Medical Center, New York, New York

PROFESSIONAL CERTIFICATIONS:

1994	Board Certified, American Board of Psychiatry and Neurology (Neurology)

PROFESSIONAL SOCIETY MEMBERSHIPS:

American Medical Association
American Academy of Neurology
American Association for the Study of Headache
National Headache Foundation
International Headache Society

HONORS AND AWARDS:

Leo M. Davidoff Award for Excellence in Teaching, Albert Einstein College of Medicine, Bronx, New York
Best Poster Presentation, Headache World 2000, London UK

OTHER PROFESSIONAL ACTIVITIES:

1990-1992	Quality Assurance Committee, Montefiore Medical Center
1992-1995	Ethics Ad Hoc Committee, American Association for the Study of Headache
1992-1994	Abstracts Co-Editor, Headache
1992-1995	Education Committee, American Association for the Study of Headache
1996-	Education Committee, American Academy of Neurology
1996-	Course Co-Director, American Association for the Study of Headache

2000- Patient Education Committee, Roosevelt Hospital Center, New York, NY
2000- Course Director, Headache in Adults, American Academy of Neurology
2000- Editor, Migraine Section, Current Pain and Headache Reports

CONSULTANT/REVIEWER:

1991 Ad Hoc Reviewer, Neurology
1992 Ad Hoc Reviewer, Cephalalgia
1993 Ad Hoc Reviewer, Headache
2001 Ad Hoc Reviewer, Journal of Anesthesiology
2001 Ad Hoc Reviewer, National Institute of Health

BIBLIOGRAPHY:

A. ORIGINAL COMMUNICATIONS:

1. Lipton RB, Newman LC, Solomon S. Aspartame as a dietary trigger in migraine. Headache1989;20:90-92.

2. Solomon S, Lipton RB, Newman LC. Nuchal features of cluster headaches. Headache 1990; 30:347-349.

3. Newman LC, Lipton RB, Solomon S. The hypnic headache syndrome. Neurology 1990; 40:1904-1905.

4. Galer BS, Lipton RB, Newman LC, Solomon S. Myocardial ischemia related to ergot alkaloids: A case report and literature review. Headache 1991; 31:446-450.

5. Lipton RB, Feraru ER, Weiss G, Chhabria M, Harris C, Aronow H, Newman LC, Solomon S. Headache in HIV-1 related disorders. Headache 1991; 31:518-522.

6. Newman LC, Gordon ML, Lipton RB, Kanner R, Solomon S. Chronic paroxysmal headache: two cases with cerebrovascular disease. Headache 1992; 32:75-76.

7. Newman LC, Gordon ML, Lipton RB, Kanner R, Solomon S. Episodic paroxysmal hemicrania: two new cases and a literature review. Neurology 1992; 42:964-966.

8. Newman LC, Lipton RB, Solomon S. Hemicrania continua: Attacks may alternate sides. Headache 1992; 32:237-238.

9. Solomon S, Lipton RB, Newman LC. Clinical features of chronic daily headache. Headache 1992; 32:325-329.

10. Solomon S, Lipton RB, Newman LC. Evaluation of the criteria for the diagnosis of chronic tension-type headache. Cephalalgia 1992; 12:365-368.

11. Newman LC, Lipton RB, Solomon S. Episodic paroxysmal hemicrania: three new cases and a literature review. Headache 1993; 33:195-197.

12. Newman LC, Lipton RB, Solomon S. Hemicrania continua: 10 new cases and a review of the literature. Neurology 1994; 44:2111-2114.

13. Solomon S, Lipton RB, Newman LC. The Site of Common Side Effects of Sumatriptan. Headache, 1997; 37:289-290.

14. Lipton RB, Lowenkoff T, Bajwa ZH, Leckie RS, Newman LC. Cardiac Cephalalgia: a malignant form of exertional headache. Neurology, 1997; 49:813-816.

15. Lipton RB, Mazer C, Newman LC, Solomon S. Sumatriptan relieves migraine like headaches associated with carbon monoxide exposure. Headache 1997; 37:392-395.

16. Newman LC, Lipton RB, Lay CL, Solomon S. An open-label pilot study of oral Sumatriptan in the intermittent prophylaxis of menstrually-associated migraines. Neurology, 1998; 51:307-309.

17. Newman LC, Steiner DS. Treatment of common headaches. What to do when it's not a migraine. Women's Primary Care, 1998; 1:753-762

18. Lay CL, Newman LC, Post-traumatic hemicrania continua. Headache. 1999:39:275-279

19. Lay CL, Newman LC. Menstrual Migraine: Approaches to Management CNS Drugs. 1999; 12:189-195

20. Solomon S, Newman LC. Chronic Daily bilateral headache responsive to indomethacin. Headache, 1999; 39:754-757

21. Lay CL, Newman LC. Identifying and treating hormonal migraine. Women's Health in Primary Care. 2000; 3:27-35

22. Mascellino AM. Lay CL, Newman LC. Stabbing headache as the presenting manifestation of intracranial meningioma: a report of two patients. Headache, 2001; 41:599-601

23. Newman LC. Manix LK. Landy S. et al. Naratriptan as short-term prophylaxis of menstrually associated migraine: a randomized, double-blind, placebo-controlled study. Headache, 2001; 41-: 248-256

24. Newman LC, Lipton RB. Migraine MLT-down: An unusual presentation of migraine in patients with aspartame-triggered headaches. Headache. 2001; 41:899-901

B. MONOGRAPHS:

1. Lipton RB, Newman LC, McLean H. Migraine: Beating the Odds. Addison-Wesley, New York, 1993.

2. Newman LC. (Editor). Avoiding common pitfalls in the diagnosis and treatment of migraine headaches. CME Audiotape Program, Annenburg Center, 1996.

3. Newman LC. (Editor). Pitfalls in managing your migraine patients. CME Audiotape Program, Medical College of Virginia, 1998.

4. Newman LC (Editor). How to Select Optimal Acute Migraine Therapy: The Neurologists Approach. Audiotape Program, 1999.

5. Newman LC, Lay CL, (Eds.) Menstruation-Associated Migraine. CME Program, Meniscus Educational Institute 1999

C. REVIEW ARTICLES AND BOOK CHAPTERS:

1. Solomon S, Lipton RB, Newman LC. Prophylactic therapy for cluster headache. J Neuropharmacology 1991; 14:116-130.

2. Solomon S, Lipton RB, Newman LC. Differential diagnosis of headache. Hospital Medicine 1991; 27(10):51-61.

3. Sands GH, Newman L, Lipton RB. Cough, exertion and other miscellaneous headaches. In S Diamond (Ed) Medical Clinics of North America 1991; 75(3):722-748.

4. Newman LC, Lipton RB, Solomon S. The hypnic headache syndrome. In: F Clifford Rose (Ed), 1991 New Advances In Migraine Research, Smith Gordon.

5. Solomon S, Lipton RB, Newman LC. Migraine: clinical features and diagnosis. Comprehensive Therapy, 1992;18:24-27.

6. Newman LC, Lipton RB, Solomon S. Taking a headache history. In: CD Tollison and RS Kunkel (Eds.) Headache: Diagnosis and Treatment. Williams and Wilkins,1993; pp.23-30.

7. Solomon S, Lipton RB, Newman LC. Tension-type headaches: Clinical symptomatology and differential diagnosis. In: CD Tollison and RS Kunkel

8. (Eds) Headache: Diagnosis and Treatment. Williams and Wilkins, 1993; pp.123-128.

9. Sands G, Newman LC, Lipton RB. Uncommon headaches. In: CD Tollison and RS Kunkel (Des) 1993; Headache: Diagnosis and Treatment. Williams and Wilkins, pp.297-308.

10. Lipton RB, Pfeiffer D, Newman LC, Solomon S. Headache in the elderly. J. of Pain and Symptom Management, 1993; 8:87-97.

10. Lipton RB, Newman LC, Solomon S. Over-the-counter medication and treatment of migraine. (Editorial) Headache, 1994;34:547-548.

11. Newman LC, Lipton RB. Prophylactic drug treatment of migraine. Seminars in Headache Management, 1996; 1(2):10-14.

12. Newman LC, Lipton RB. Cluster headache variants. Seminars in Headache Management, 1996; 1(3): 4-9.

13. Lipton RB, Newman LC. Migraine. In Kanner R (ed), Pain Management Secrets, 1997; Hanley and Belfus, Inc., Philadelphia, Pennsylvania. pp 41-49.

14. Lipton RB, Newman LC. Tension-type headache. In Kanner R (ed), Pain Management Secrets, 1997;Hanley and Belfus, Inc., Philadelphia, Pennsylvania. pp 37-40.

15. Newman LC, Lipton RB. Cluster headache. In Kanner R (ed), Pain Management Secrets, 1997; Hanley and Belfus, Inc., Philadelphia, Pennsylvania. pp 50-53.

16. Newman LC, Lipton RB. Paroxysmal hemicranias. In Kanner R (ed), Pain Management Secrets, 1997;Hanley and Belfus Inc., Philadelphia, Pennsylvania. pp 54-56.

17. Newman LC, Lipton RB. The paroxysmal hemicranias. In Goadsby PJ and Siberstein SD (Eds.) 1997; Headache, Butterworth-Heinemann Ltd., London, England, pp.243-254.

18. Newman LC, Shinnar S. Treatment of headaches in adolescence. In Friedman SB, Fischer MM, Schonberg SK, Alserman EM. (Eds). 1998; Comprehensive Adolescent Health Care, 2nd Edition, Mosby, St. Louis pp. 493-500.

19. Newman LC, Lipton RB. Emergency department evaluation of headache. In Feske, SK Wen PY. (Eds) 1998;Neurologic Clinics, Saunders, Philadelphia pp. 285-303.

20. Newman LC. The Man with Never-Ending Headaches. In Rapoport AM Sheftell FD and Purdy RA (Eds.) 1999; Advanced Therapy of Headache. B.C. Decker, St. Louis.

21. Berliner R. Solomon S, Newman LC, Lipton RB. Migraine: Clinical features and diagnosis. Compr Ther: 1999; 25: 397-402.

22. Newman LC, Lipton RB. Ergotamine tartrate. In Spence PS, Schaumberg HH Experimental and Clinical Neurotoxicology, In Oxford University Press, New York pp. 535-537, 2000.

23. Newman LC Effective management of ice pick pains, SUNCT, and episodic and chronic paroxysmal hemicrania. Current Pain Headache Rep, 2001;5:292-299:

24. Newman LC, Goadsby P, Lipton RB. Cluster and related headaches. In Matthew N. (Ed), Medical Clinics of North America 2001; 85 (4): 997-1016

25. Solomon S, Newman LC. Episodic Tension-Type Headaches. In: Silberstein SD, Lipton RB, Dalessio DJ (Eds). 2001; Wolff's Headache and other Head pain, Oxford University Press; New York pp. 238-246

26. Newman LC, Goadsby PJ. Universal Primary Headache Disorders In Silberstein SD, Lipton RB, Dalessio DJ (Eds). 2001; Wolff's Headache and other Head pain, Oxford University Press, New York, pp. 310-321

27. Newman LC, Solomon S. Infectious, stoxic and metabolic Headache. In Silberstein SD, Lipton RB, Dalessio DJ (Eds). 2001; Wolff's Headache and other Head Pain, Oxford University Press, New York pp. 434-446

D. ABSTRACTS, LETTERS, SCIENTIFIC PRESENTATIONS AND BOOK REVIEWS:

1. Lipton RB, Newman LC, Cohen J, Solomon S. Aspartame as a dietary factor in headache. Neurology 1998; 38(3):351. Presented at the meeting of the American Academy of Neurology.

2. Lipton RB, Newman LC, Solomon S. Aspartame and headache (letter). New England Journal of Medicine 1988; 318:1200.

3. Lipton RB, Newman LC, Solomon S. Placebo-control studies of dietary factors in migraine. Headache 1988; 28(4):315. Presented at the meeting of the American Study for the Study of Headache.

4. Solomon S, Lipton RB, Newman LC. The neck and cluster headache. Headache 29:311, 1989. Present at the meeting of the American Association for the Study of Headache.

5. Solomon S, Lipton RB, Newman LC. Nuchal features of cluster headache. Cephalalgia 1989; 9(Suppl 10):201-202.

6. Newman LC, Lipton RB, Solomon S. The hypnic headache syndrome. Neurology 1990; 40(Suppl 1):436. Present at the meeting of the American Academy of Neurology.

7. Newman LC, Lipton RB, Solomon S. Hypnic headaches (letter). Headache 1990; 30: 227.

8. Solomon S, Lipton RB, Newman LC. Spreading depression marches on (letter). Headache 1990; 30:741.

9. Newman LC, Gordon M, Lipton RB, Kanner R. Episodic paroxysmal hemicrania. Cephalalgia 1991; 11(Suppl 11):268-269. Presented at the meeting of the International Headache Congress, Washington DC.

10. Solomon S, Lipton RB, Newman LC. Evaluation of the criteria of chronic tension-type headache. Cephalalgia 1991; 11(Suppl 11):323-324. Presented at the meeting of the International Headache Congress, Washington, DC.

11. Newman LC. A multidisciplinary approach to headache. (Book review) J of Pain and Symptom Management 1992; 6:4-5.

12. Newman LC, Lipton RB, Solomon S. Episodic paroxysmal hemicrania: three new cases. Neurology 1992; 42(Suppl 3):430. Presented at the meeting of the American Academy of Neurology, San Diego, California.

13. Newman LC, Lipton RB, Russell M, Solomon S. Some comments on hemicrania continua and episodic paroxysmal hemicrania (letter). Headache 1993; 33:44-5.

14. Newman LC, Lipton RB, Solomon S. Episodic paroxysmal hemicrania (letter). Neurology, 1993; 43: 1446.

15. Newman LC, Lipton RB, Solomon S. Hemicrania continua: 5 new cases and an literature review. Neurology 1993; 43(Suppl 2):327,1993. Presented at the meeting of the American Academy of Neurology, New York, New York.

16. Newman LC, Lipton RB, Solomon S. Hemicrania continua: 7 new cases and a literature review. Headache 1993; 5:267. Presented at the Scientific Meetings of The American Association for the Study of Headache, San Francisco, California, 1993.

17. Tension-type Headaches (Book review). Frontiers in Headache Research. Vol. 3 Headache 1994; 34:175.

18. Lipton RB, Newman LC, Solomon S. Cluster headache and CPD: Diagnostic difficulties. Neurology, 1994; 44:2215-2216.

19. Newman LC, Lipton RB, Solomon S, Stewart WF. Daily headaches in a population-based sample: results from the American Migraine Study. Headache, 1994;5:295. Presented at the 36th Annual Scientific Meeting of the American Association for the Study of Headache, June 24, 1994.

20. Lipton RB, Solomon S, Newman LC, Sheftell FD. Gastrointestinal symptoms in migraine: results from the AASH-Gallup Survey. Headache, 1995; 35:563. Presented at the 37th Annual Meeting of the American Association for the Study of Headache, June 23, 1995.

21. Newman LC, Lipton RB, Solomon S. Hemicrania continua (letter). Neurology, 1995;45:1948-1949.

22. Lipton RB, Newan LC, Solomon S. Over-the Counter Medication and the Treatment of Migraine. Headache, 1994; 34:547-548.

23. Newman LC, Solomon S, Lipton RB. Hemicrania Continua (letter). Neurology, 1995; 45:2302-2303.

24. Solomon S, Newman LC. Chronic paroxysmal hemicrania in child? Headache, 1995;35:234.

25. Solomon S, Newman LC. Abstracts and citations (letter) Headache, 1995; 35: 567.

26. Newman LC, Lipton RB, Solomon S. An open-label pilot study of oral Sumatriptan in the intermittent prophylaxis of menstrually associated migraine. Headache, 1996; 36:272-273. Presented at the 38th Annual Scientific Meeting of the American Association for the Study of Headache, May 31, 1996.

27. Newman LC, Solomon S, Lipton RB. Post-traumatic hemicrania continua. Neurology,1997; 48: A23. Presented at the 49th Annual Meeting of the American Academy of Neurology, April 15, 1997.

28. Newman LC, Lipton RB, Lay LC, Solomon S. An open-label pilot study of oral Sumatriptan in the intermittent prophylaxis of menstrual migraine. Cephalalgia, 1997; 7 (3): 437. Presented at the International Headache Society Meeting, Amsterdam, Holland, June 12, 1997.

29. Solomon S, Newman LC. Classification of Post-traumatic migraine. Neurology 1997; 48:A261. Presented at the 49th Annual Meeting of the American Academy of Neurology, April 15, 1997.

30. Newman LC, Lipton RB, Lay LC, Solomon S. An open-label pilot study of oral sumatriptan in the intermittent prophylaxis of menstrual migraine. Headache 1998 Quarterly. Presented at the Participating Physician's Approach to the Difficult Headache Patient. Palm Springs, California February 20, 1998.

31. Newman LC, Steiner DS, Kazmi MM, Berliner R. Zolmatriptan for the acute treatment of migraine in sumatriptan non-responders: Open-label pilot study. Headache, 1998; Volume 38. Presented at the 40th Annual Scientific Meeting of the American Association for the Study of Headache, San Francisco, June 26, 1998.

32. Newman LC, Steiner DS. Divalproex Sodium (Depakote) as migraine prophylaxis in patients with cognitive side effects to prior treatment with antimigraine agents: A retrospective chart review. Headache Quarterly, 1998. Presented at the Practicing Physicians Approach to the Difficult Headache Patient, Orlando, Florida, June 1998.

33. Newman LC, Steiner DS. Divalproex Sodium (Depakote) as migraine prophylaxis in patients' unresponsive to prior treatment with antidepressants agents: A retrospective chart review. Headache Quarterly, 1998. Presented at the Practicing Physicians Approach to the Difficult Headache Patient, Orlando, Florida, 1998.

34. Solomon S, Newman LC. Chronic daily bilateral headache responsive to indomethacin. Headache 1998; 38:406.

35. Solomon S, Newman LC. Unusual indomethacin responsive headaches. Cephalalgia 1998; 18:411.

36. Newman LC. A pilot study of oral sumatriptan as intermittent prophylaxis of menstruation –related migraine. (letter). Neurology 1999; 52:1301-1302.

37. Newman LC, Lay CL, O'Connor KA, Russell M. Lack of Cross-Reactivity of Sumatriptan in patients allergic to Sulfonamides: A Retrospective chart review. Headache 1999; 39; 372.

38. Newman LC, Mannix LK, Landy SH. Naratriptan as prophylaxis for menstrually associated migraine: A randomized double blind, placebo controlled study. Neurology 2000; 54 (7 Suppl 3): A14. Presented at the 52nd Annual meeting of the American Academy of Neurology, San Diego, CA May 2000.

39. Newman LC, Mannix LK. Naratriptan as prophylaxis for menstrually associated migraine: /a randomized double blind, placebo controlled study. Cephalalgia 2000; 20 (4): 424. Presented at Headache World 2000, London UK, September 2000.

E. INVITED LECTURES:

1. The Pharmacologic Therapies of Migraine Headache. The New Jersey Pharmaceutical Association, Cranford, New Jersey. January 20, 1993.

2. Current Concepts in the Diagnosis and Treatment of Headache. The New Jersey Pharmaceutical Association, Runnemeade, New Jersey. January 21, 1993.

3. Migraine: Epidemiology, Pathophysiology, Diagnosis and Treatment. Presented at The Eight Annual Meeting of The Tampa General Hospital Pharmaceutical Committee, Tampa, Florida. January 30, 1993.

4. Headache Overview. The Arnold and Marie Schwartz College of Pharmacy, Queens, New York. May 2, 1993.

5. The Pharmacists Role in the Treatment of Migraine. The Long Island Society of Hospital Pharmacists, Westbury, New York. June 17, 1993.

6. Update on Migraine. Northern New Jersey Society of Hospital Pharmacists, Tenfly, New Jersey. September 23, 1993.

7. Advances In The Treatment of Migraine. Middlesex County Pharmaceutical Association, Denville, New Jersey. October 7, 1993.

8. The Pharmacists Role In the Treatment of Headache. Morris-Sussex Pharmacy Association, Denville, New Jersey. October7, 1993.

9. Migraine: Diagnosis and Treatment. Indian Medical Association, Potomac, Maryland. October 23, 1993.

10. Update on Migraine Therapy. Van Buren County Medical Society, South Haven Community Hospital, South Haven, Michigan. October 30, 1993.

11. The Pharmacist Role in the Management of Headache. Rutgers University, Piscaraway, New Jersey. January 21, 1994.

12. Migraine: Epidemiology, Pathophysiology, Diagnosis and Treatment. The Society for Women's Physicians, Short Hills, New Jersey. April 12, 1994.

13. Epidemiology of Migraine. Presented at the Sixth Annual Congress of Managed Health Care, Washington, DC. April 13, 1994.

14. The relationship between Headache and Sleep. American Association for the Study of Headache, Scottsdale AZ. November 1997.

15. The relationship between Headache and Sleep. American Association for the Study of Headache, Scottsdale AZ. November 1998.

16. Headaches of Short Duration. American Association for the study of Headache. Scottsdale AZ, November 1999.

17. Evaluation of headaches: the Neurologist Approach. Diamond Headache Meeting, Palm Springs CA, 1999.

18. Headaches of Short Duration. American Academy of Neurology, San Diego CA, 2000.

19. Neurologic Cross-Fire. American Academy of Neurology, San Diego CA. 2000.

20. The Trigeminal Autonomic Cephalalgias. American Headache Society, Scottsdale AZ, 2000.

21. In patient treatment Strategies. American Headache society, Scottsdale AZ, 2000.

22. Chronic Daily and Tension-type Headache. Diamond Headache Meeting. Palm Springs CA, 2000.

23. Migraine Co-Morbidity. American Headache Society, Miami, FL, 2001.

24. Headache of Short duration. American Headache Society, Miami, Florida, 2001.

25. Headache of Short Duration. American Headache Society, Scottsdale AZ, 2001.

26. In-patient treatment Strategies. American Headache Society, Scottsdale AZ, 2001

27. Chronic Daily and Tension-type Headache. Diamond Headache Meeting. Palm Springs CA, 2001.

28. Headache of Short Duration. American Academy of Neurology. Philadelphia PA 2001.

LAWRENCE C. NEWMAN, M.D. – Is an Associate Professor of Neurology at the Albert Einstein College of Medicine and Director of St. Luke's-Roosevelt and Beth Israel Medical Center's Headache Institute. He is a Diplomat of the American Board of Psychiatry and Neurology, being board certified in Neurology. Dr. Newman serves on the Education Committee for the American Association for the Study of Headache and the American Academy of Neurology, and is a member of the American Association for the Study of Headache, the National Headache Foundation, and the International Headache Society. He is an Ad-Hoc reviewer for the journals Headache, Cephalalgia, and Neurology. Dr. Newman was a resident and chief resident in Neurology at the Albert Einstein College of Medicine in the Bronx, New York, and completed a formal Headache Fellowship at the Montefiore Headache Unit. He was the Director of the Montefiore Headache Unit from 1996-1997.

Dr.Newman is on the Advisory Boards and has conducted clinical research for Glaxo Smith Klein, Astra Zeneca, Novartis, Abbott, Pfizer, Bristol Meyers Squibb, and Merck. Dr. Newman is an experienced lecturer who has published extensively on the diagnosis and treatment of unusual headache disorders. He is listed in The Best Doctor's in New York and Who's Who in Science and Medicine.

19TH
EDITION

Remington: Practice of

ALFONSO R GENNARO

Chairman of the Editorial Board
and Editor

The Science and Pharmacy

1995

MACK PUBLISHING COMPANY
Easton, Pennsylvania 18042

Library of Congress Catalog Card No. 60-53334

ISBN 0-912734-04-3

The use of structural formulas from USAN and the USP Dictionary of Drug Names is by permission of The USP Convention. The Convention is not responsible for any inaccuracy contained herein.

NOTICE—This text is not intended to represent, nor shall it be interpreted to be, the equivalent of or a substitute for the official United States Pharmacopeia (USP) and/or the National Formulary (NF). In the event of any difference or discrepancy between the current official USP or NF standards of strength, quality, purity, packaging and labeling for drugs and representations of them herein, the context and effect of the official compendia shall prevail.

Printed in the United States of America by the Mack Printing Company, Easton, Pennsylvania

CHAPTER 68

Local Anesthetics

Glen R Hanson, DDS, PhD

Professor of Pharmacology
College of Pharmacy and School of Medicine
University of Utah
Salt Lake City UT 84112

Local anesthetics reversibly block impulse conduction in any part of the nervous system and in all nerves, including sensory, motor and autonomic types. They often are used to produce a transient loss of sensation in a circumscribed area of the body without causing a general loss of consciousness. This action can be used to block pain sensation—or sympathetic vasoconstrictor impulses—to specific areas of the body. Hence, local anesthetics are used to prevent pain in surgical procedures, dental manipulations, injury and disease. The synthetic local anesthetic agents may be divided into two groups: the slightly soluble compounds and the soluble compounds. The *slightly soluble* local anesthetics are used only for surface (topical) application, since their slow absorption renders them safe for use on ulcers, wounds and mucous surfaces. The anesthesia which they induce is not as complete as that induced by soluble compounds, but the duration is longer. Many soluble anesthetics also may be used for topical anesthesia. On the other hand, only *soluble* local anesthetics of relatively low toxicity should be injected.

Local anesthesia induced by injectable agents is designated according to the technique or anatomic site of the injection. *Infiltration anesthesia* refers to injection directly into the area that is painful or to be subjected to surgical trauma. *Field block* is accomplished by administering the local anesthetic to a region of the nerve proximal to the site to be anesthetized. *Peripheral nerve block*, commonly called *regional anesthesia*, places the anesthetic agent in direct contact with the nerve or nerve plexus. *Paravertebral nerve block* places the anesthetic agent in direct contact with the nerve as it exits the intervertebral foramina. *Epidural* and *caudal blocks* are similar; caudal block is an epidural block in the caudal region. *Subarachnoid block*, commonly called *spinal anesthesia*, but more correctly *spinal analgesia*, requires that the anesthetic be placed within the subarachnoid space so that the anesthetic agent mixes with spinal fluid. The use of a hyperbaric (heavy) solution or hypobaric (light) solution and proper positioning of the patient on the operating table permits manipulation of anesthesia for various body areas.

Local anesthetics prevent both the generation and the conduction of the nerve impulse. The excitable membrane of nerve axons maintains a transmembrane potential of −90 to −60 mV. During excitation, the sodium channels open and a fast inward sodium current quickly depolarizes the membrane toward the sodium equilibrium potential (+40 mV). As a result of depolarization, the sodium channels close (inactivate) and potassium channels open. The outward flow of potassium repolarizes the membrane toward the potassium equilibrium potential (−95 mV); repolarization returns the sodium channels to the rested state. The transmembrane ionic gradients are maintained by the sodium pump.

When increasing concentrations of a local anesthetic are applied to a nerve fiber, the threshold for excitation increases, the impulse conduction slows, the rate of rise of the action potential declines, the action potential amplitude decreases and, finally, the ability to generate an action potential is abolished. All these effects result from the binding of the local anesthetic to sodium channels which in turn blocks the transient permeability to sodium. If the sodium current is blocked over a critical portion of nerve, propagation of an impulse over the blocked area is no longer possible.

When infiltration, conduction or regional techniques are employed, both nerve fibers and nerve endings are anesthetized. The ease with which a nerve fiber may be anesthetized is related to its type and size. Although there are exceptions, large myelinated nerves usually require a greater concentration of anesthetic solution and more time to be blocked than do small nonmyelinated fibers. Accordingly, small nerve fibers concerned with vasoconstriction, temperature and surface pain are anesthetized most easily, whereas large fibers associated with the sensation of touch, pressure, deep pain and the sensations from joints and tendons are anesthetized with more difficulty. In spinal anesthesia, it is probable that both sensory and motor nerve fibers are anesthetized. In surface (topical) anesthesia, the sensory nerve endings are the chief nerve structures affected.

The nerve-blocking action of the local anesthetics is pH sensitive. Because these drugs generally are marketed as water-soluble salts, the injected solutions are mildly acidic. In order to block nerve activity, the local anesthetic must become deprotonated and diffuse through cellular membranes to reach its intracellular site of action. However, because the cationic species is the form of the local anesthetic which interacts preferentially with the sodium channels, molecules which have crossed the membranes must be protonated again to be effective. Changes in extracellular pH can disrupt the balance between protonated and deprotonated forms and interfere with local anesthetic activity. This can occur in areas of tissue damage or inflammation or following multiple administrations of the acidic local anesthetic solutions.

The duration of action of a local anesthetic is proportional to the time during which it is in actual contact with nervous tissues. Consequently, procedures that help localize the drug at the nerve prolong anesthesia. Cocaine itself constricts blood vessels, prevents its own absorption and has a duration of action longer than most local anesthetics. A vasoconstrictor drug, such as epinephrine, norepinephrine, levonordefrin, is included frequently in local anesthetic solutions. The presence of one of these drugs in the local anesthetic solution retards absorption of the local anesthetic solution, thereby reducing its systemic toxicity, increasing its duration of action and increasing its efficiency by decreasing the volume of solution required. The pressor potency relative to epinephrine (shown in parentheses), maximal total dose and usual concentration are as follows: epinephrine (1), 0.2 mg, 1:50,000 to 1:200,000; norepinephrine (0.6), 0.34 mg, 1:30,000 and levonordefrin (0.5), 1 mg, 1:20,000. While vasoconstriction helps prolong the effects of the local anesthetics, it can be problematic in areas with restricted blood supply. Consequently, it is inadvisable to inject local anesthetics with vasoconstrictors around the base of fingers, toes or the penis. Some of the vasoconstrictor may be absorbed systemically causing adverse effects associated with their sympathomimetic actions. Such side effects can be particularly dangerous in the presence of cardiovascular disease or concurrent

30 to 36 hr. It is contraindicated in patients hypersensitive to it and to aspirin, phenacetin or caffeine. The drug should not be used during pregnancy unless, in the physician's judgment, the potential benefits exceed the potential hazards. The most frequent adverse effects are dizziness, sedation, nausea and vomiting. Other adverse reactions include constipation, abdominal pain, skin rashes, light-headedness, headache, weakness, euphoria, dysphoria and minor visual disturbances. The chronic ingestion of 800 mg/day has caused toxic psychoses and convulsions. The depressant effects of propoxyphene may be additive with those of other depressant drugs, such as alcohol, tranquilizers and sedative-hypnotics. Moreover, a number of deaths have been reported in patients on excessive doses, either alone or in combination with other CNS depressant drugs. Since both psychological and physical dependence have been induced with this agent, it should be prescribed with the same degree of caution as codeine.

Drowsiness or dizziness may occur which may impair ability to drive or perform other tasks requiring alertness. It is not recommended for children.

Dose—**32** to **390 mg** a day; *usual*, **65 mg** 6 times a day as necessary.

Dosage Form—Capsules: 32 and 65 mg.

Propoxyphene Napsylate

Benzeneethanol, [*S*-(*R**, *S**)]-α-[2-(dimethylamino)-1-methylethyl]-α-phenyl-, propanoate (ester), compound with 2-naphthalenesulfonic acid (1:1) monohydrate; Darvon-N (*Lilly*)

[26570-10-5] $C_{22}H_{29}NO_2.C_{10}H_8O_3S.H_2O$ (565.72); *anhydrous* [17140-78-2] (547.71).

For the structure of the base, see *Propoxyphene Hydrochloride*.

Preparation—*Propoxyphene* is reacted with an equimolar quantity of aqueous 2-naphthalenesulfonic acid and the salt is crystallized therefrom.

Description—White, bitter, crystalline powder; essentially no odor; melts in a 4° range between 158° and 165°.

Solubility—1 g in 10,000 mL of water, 15 mL of alcohol or 10 mL of chloroform; soluble in ether.

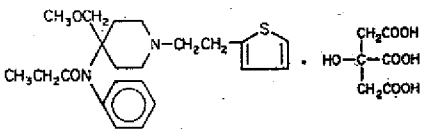
Uses—Actions, uses and precautions are the same as *Propoxyphene Hydrochloride*, except that, because of its larger molecular weight, a dose of 100 mg is required instead of the 65 mg dose of the hydrochloride. This compound permits more stable liquid and tablet dosage forms because of its very slight solubility in water.

Dose—*Usual*, **100 mg** every 4 hr as needed for pain. Do not exceed 600 mg per day.

Dosage Forms—Oral Suspension: 10 mg/mL; Tablets: 100 mg.

Sufentanil Citrate

Propanamide, *N*-[4-(methoxymethyl)-1-[2-(thienyl)ethyl]-4-piperidinyl]-*N*-phenyl-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1); Sufenta (*Janssen*)



[60561-17-3] $C_{22}H_{30}N_2O_2S.C_6H_8O_7$ (578.68).

Preparation—*Arzneimittel-Forsch 26:* 1521, 1976.

Description—White crystals; melts about 97°.

Uses—A strong opioid analgesic. Its analgesic potency is 5 to 12 times that of fentanyl on a weight basis. High doses can cause amnesia and a loss of consciousness. It is used for balanced anesthesia in general surgery as an adjunct to nitrous oxide and oxygen. It also may be used for induction of surgical anesthesia and as the sole anesthetic agent with a muscle relaxant and oxygen for cardiovascular and neurosurgical procedures. Given intravenously it is metabolized rapidly (elimination half-life, 2.4 hr). The volume of distribution is 2.5 L/kg; 92.5% is bound to plasma protein; plasma clearance is 0.8 L/min. The most common adverse effects include respiratory depression and skeletal muscle rigidity. The rapid intravenous administration of sufentanil may induce a general increase in muscle tone, including chest-wall spasm. Other adverse effects include bradycardia, hypotension and hypertension. After low doses recovery time is about the same as that for fentanyl. Sufentanil is a *Schedule II* drug under the *Federal Controlled Substances Act*.

Dose—*Adult, intravenous, general surgery:* **1 to 2 μg/kg** with nitrous oxide/oxygen; *maintenance*, **10 to 25 μg** as needed. *Cardiovascular or neurological surgery*: **2 to 8 μg/kg** or more with oxygen and a nondepolarizing (curariform) muscle relaxant; *maintenance*, 25 to 50 μg as needed. *Children 2 to 12 yr, cardiovascular surgery*: 10 μg/kg or more with oxygen only. *Children under 2 yr:* no dose has been established.

Dosage Form—Solution: 50 μg/mL in 2, 5, 10, 20 and 50 mL.

Narcotic Analgesic Combinations

Some examples of narcotic analgesic combinations (with mg/unit provided) as as follows:

Codeine Phosphate and Acetaminophen [Tylenol with Codeine #1 (*McNeil*); Tylenol with Codeine Elixir (*McNeil*); Tylenol with Codeine #2 (*McNeil*); Phenaphen with Codeine #2 (*Robins*); Papadeine #3 (*Vangard*); Tylenol with Codeine #3 (*McNeil*); Phenaphen with Codeine #3 (*Robins*); Phenaphen 650 with Codeine (*Robins*); Papadeine #4 (*Vangard*); Tylenol with Codeine #4 (*McNeil*); Phenaphen with Codeine #4 (*Robins*)]—7.5 and 300; 12 and 120; 15 and 300; 15 and 325; 30 and 300; 30 and 325; 30 and 650; 32 and 325; 60 and 300; 60 and 325 mg, respectively.

Codeine Phosphate and Aspirin [Empirin with Codeine #2 (*Burroughs Wellcome*); Empirin with Codeine #3 (*Burroughs Wellcome*); Empirin with Codeine #4 (*Burroughs Wellcome*)]—15 and 325; 30 and 325; 60 and 325 mg, respectively.

Codeine Phosphate, Acetaminophen and Caffeine [Codalan #1, 2 and 3 (*Lannett*)]—8, 500 and 300; 15, 500 and 30; 30, 500 and 30 mg, respectively.

Codeine Phosphate, Aspirin, Caffeine and Butalbital [Fiorinal with Codeine (*Sandoz*)]—30, 325, 40 and 50 mg, respectively.

Dihydrocodeine Bitartrate, Aspirin and Caffeine [Synalgos-DC (*Wyeth*)]—16, 365.4 and 30 mg, respectively.

Hydrocodone and Acetaminophen [Amacodone (*Trimen*); Dolacet (*Hauck*); Hydrocet (*Carnrick*); Vicodin (*Knoll*); Zydone (*Dupont*)]—5 and 500 mg, respectively.

Meperidine Hydrochloride and Acetaminophen [Demerol APAP (*Winthrop-Breon*)]—50 and 300 mg, respectively.

Meperidine Hydrochloride and Promethazine Hydrochloride [Mepergan (*Wyeth*); Mepergan Fortes (*Wyeth*)]—25 and 25; 25 and 50 mg, respectively.

Morphine Sulfate and Atropine Sulfate [Morphine and Atropine Injection (*Beecham*)]—16 and 0.4 mg/mL, respectively.

Oxycodone Hydrochloride and Acetaminophen [Percocet (*Dupont*); Tylox (*McNeil*)]—5 and 325; 5 and 500 mg, respectively.

Propoxyphene Hydrochloride and Acetaminophen [Dolene AP-65 (*Lederle*); Wygesic (*Wyeth*)]—65 and 650 mg, respectively.

Propoxyphene and Aspirin [Darvon with ASA (*Lilly*)]—65 and 325 mg, respectively.

Propoxyphene Hydrochloride, Aspirin and Caffeine [Darvon Compound-65 (*Lilly*)]—65, 389 and 32.4 mg, respectively.

Propoxyphene Napsylate and Acetaminophen [Darvocet-N 50 (*Lilly*); Darvon-N 100 (*Lilly*); Doxapap-N (*Major*); Propacet (*Lemmon*)]—50 amd 325; 100 and 650 mg, respectively.

Propoxyphene Napsylate and Aspirin [Darvon-N with ASA (*Lilly*)]—100 and 325 mg, respectively.

Analgesics, Antipyretics and Anti-Inflammatories

The analgesic, antipyretic and antiinflammatory drugs include a small, heterogeneous group of compounds which, unlike those presented in the two preceding sections, are without significant addiction liability and, therefore, are not subject to regulation under the *Controlled Substances Act*. Many of these agents affect pain, fever and inflammation and are referred to as the nonsteroidal antiinflammatory drugs (NSAIDs). Consequently, they are used widely for minor aches and pains, headaches and the general feeling of malaise that accompanies febrile illnesses, and to alleviate symptoms of rheumatic fever, arthritis, gout and other musculoskeletal disturbances. Several agents (allopurinol, colchicine, probenecid, etc) do have pain-relieving properties in various conditions (gout, arthritis, etc), but since they are of no value in other types of pain, they cannot be classed as true analgesic drugs and will be discussed in a separate section.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

The number of NSAIDs continues to increase. In addition to aspirin-like drugs, the NSAIDs available in this country include meclofenamate sodium, phenylbutazone, indomethacin, piroxicam, sulindac and tolmetin for the treatment of

arthritis; mefenamic acid for analgesia; and ibuprofen, fenoprofen flurbiprofen, diclofenac, etodolac, ketorolac and naproxen for both analgesia and arthritis. Ibuprofen, mefenamic acid and naproxen are used also for the management of dysmenorrhea. For the most part, the newer nonsalicylate NSAIDs have similar pharmacological properties with some differences in their pharmacokinetic properties (see Table 3). The principal mechanism of action for all NSAIDs appears to be inhibition of prostaglandin synthesis by blocking the activity of the precursor enzyme, cyclooxygenase. Their actions on prostaglandins likely account for many of the side effects of the NSAIDs. Although, in general, there is little difference between the efficacy of different NSAIDs, some patients may respond to one agent better than another. This is difficult to predict and often requires trial and error to find the most suitable drug.

The clinical usefulness of NSAIDs is restricted by a number of adverse effects. Phenylbutazone has been implicated in hepatic necrosis and granulomatous hepatitis; and sulindac, indomethacin, ibuprofen and naproxen with hepatitis and cholestatic hepatitis. Transient increases in serum aminotransferases, especially alanine aminotransferase, have been reported. All of these drugs, including aspirin, because of their inhibition of prostaglandins, can interfere with regulation of glomerular filtration and renal sodium and water excretion. Thus, the NSAIDs can cause fluid retention and decrease sodium excretion, followed by hyperkalemia, oliguria and anuria. Moreover, all of these drugs can adversely affect the stomach and even cause peptic ulceration. Other side effects include diarrhea with meclofenamate; tinnitis with aspirin; headache with indomethacin and upper abdominal pain with ketoprofen, meclofenamate and tolmetin. The ranking of NSAIDs according to toxicity shows indomethacin, tolmetin, melofenamate and ketoprofen to be the most toxic with coated or buffered aspirin and ibuprofen the least.

Blood dyscrasias associated with NSAIDs are rare, but death has been attributed to the use of these drugs. All of them can interfere with platelet function and may cause bleeding in patients taking anticoagulants. In addition, agranulocytosis or aplastic anemia have been reported in patients on indomethacin, ibuprofen, fenoprofen, naproxen, tolmetin and piroxicam. Phenylbutazone has caused agranulocytosis and aplastic anemia, especially in the elderly, and may cause leukemia.

Other adverse effects attributed to these drugs include dermatitis and allergic reactions as well as CNS effects, such as sedation, agitation, headaches and tinnitis. Patients taking these drugs for long periods of time should have periodic white cell counts and determinations of serum creatinine levels and hepatic enzyme activities.

Table 3—Properties of Nonsalicylate NSAIDs

Nonsalicylate NSAIDs ($t_{1/2}$ hr)	Uses: Analgesic Onset (hr)	Uses: Analgesic Duration (hr)	Uses: Antiinflammatory Onset (days)
Propionic acids			
Fenoprofen (2–3)	—	—	2
Flurbiprofen(3–9)	—	—	NAv[a]
Ibuprofen (1.8–2.5)	0.5	4–6	≤7
Ketoprofen (2–4)	NAv[a]	NAv[a]	NAv[a]
Naproxen (12–15)	1	≤7	≤7
Acetic acids			
Diclofenac (1–2)	—	—	NAv[a]
Etodolac (~7)	0.5	4–12	—
Indomethacin (4.5)	0.5	4–6	≤7
Ketorolac (2.4–8.6)	0.15	≤6	—
Sulindac (7.8)	—	—	≤7
Tolmetin (1–2)	—	—	≤7
Fenamates			
Meclofenamate (2)	NAv[a]	NAv[a]	several days
Mefenamic acid (2–4)	NAv[a]	NAv[a]	—
Oxicam			
Piroxicam (30–86)	1	48–72	7–12
Others			
Nabumetone (22–30)	—	—	NAv[a]

[a] NAv—information not available.

Amodiaquine—RPS-17, page 1217.

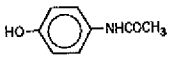
Salicylate-Like NSAIDs

The salicylate group of analgesics and antipyretics are by far the most commonly employed. Indeed, these are consumed at a rate in excess of 10,000 tons annually. In general, salicylates are *contraindicated* in hypersensitive individuals and in those with gastrointestinal disturbances, particularly hemorrhaging ulcers. They also should be used with caution in patients on anticoagulant therapy and avoided in patients on uricosurics. The *salicylates interact* with a wide variety of agents, some of which are important clinically while others are largely of theoretical interest. Nevertheless, the well-informed pharmacist will acquaint himself with the potential interactions between salicylate drugs and;

Antidiabetic agents (increased hypoglycemia).
Oral anticoagulants (displacement of anticoagulants from protein binding sites, increased anticoagulant effect).
Uricosuric agents (relative effect of large and small doses of salicylates).
Antiarthritic drugs (may lower plasma concentrations of these agents).
Alcohol (which enhances gastrointestinal bleeding).
Tetracycline (may complex with buffering agent in some aspirin products).
Other drugs (see Chapter 105).

Acetaminophen

Acetamide, *N*-(4-hydroxyphenyl)-, *N*-Acetyl-*p*-aminophenol; *p*-Acetamidophenol; (*Various Mfrs*)



4′-Hydroxyacetanilide [103-90-2] $C_8H_9NO_2$ (151.16).

Preparation—*p*-Nitrophenol is reduced and the resulting *p*-aminophenol is acetylated by heating with a mixture of acetic anhydride and glacial acetic acid. The crude product may be purified by recrystallization from an ethanol–water mixture.

Description—White, odorless, crystalline powder; slightly bitter taste; melts about 170°; pH (saturated solution) 5.3 to 6.5; pK_a 9.51.

Solubility—1 g in 70 mL water, 20 mL boiling water, 10 mL alcohol, 50 mL chloroform, 40 mL glycerin; slightly soluble in ether.

Uses—An effective antipyretic and analgesic that exerts its clinical effects by a mechanism similar to that of the salicylates. It is a major metabolite of phenacetin, a *p*-aminophenol-derived analgesic no longer available in the US due to its association with analgesic nephropathy. It produces antipyresis by acting on the hypothalamic heat-regulating center and analgesia by elevating the pain threshold. It is effective in the treatment of a wide variety of arthritic and rheumatic conditions involving musculoskeletal pain as well as the pain of headache, dysmenorrhea, myalgias and neuralgias. It also is useful in diseases accompanied by pain, discomfort and fever, such as the common cold and other viral infections. It is useful particularly as an analgesic-antipyretic in patients who experience untoward reactions to aspirin. It rarely induces untoward effects in therapeutic doses and usually is well-tolerated by aspirin-sensitive patients. Rarely, a sensitivity reaction may occur; in this case the drug should be stopped. Acetaminophen frequently is combined with other drugs, such as caffeine and aspirin. The value of such combinations is questionable. However, acetaminophen combined with opiates, such as codeine and oxycodone does enhance analgesic potency. It lacks the anti-inflammatory action of the salicylates; hence, it is of only limited usefulness in inflammatory rheumatic disorders and often is not considered an NSAID agent. It does not produce the methemoglobinemia, agranulocytosis and anemia which sometimes result from long-continued use of acetanilid and phenacetin. Unlike aspirin, acetaminophen does not antagonize the effects of uricosuric agents. Although large doses have been reported to potentiate anticoagulants, therapeutic doses have no effect on prothrombin time.

Absorption of the drug after oral administration is rapid and peak plasma levels are reached in 30 to 120 min. The therapeutic half-life is approximately 3 hr. Approximately 2% is excreted unchanged in the